A Review on Epilepsy: Exploring the Classification, Metabolic Foundation, and Genetic Aspects of Epileptic Disorder

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ABSTRACT

Epilepsy is a prominent neurological disorder caused by a range of factors, including epilepsy-associated genes, hereditary variables, environmental factors such as oxidative stress and depression, and inflammatory molecules that influence it. Worldwide, more than 65 million individuals are afflicted by epilepsy. The majority of individuals with epilepsy live in nations with low to middle-income levels. In Pakistan, the incidence of epilepsy is at 10 cases per 1000 inhabitants. There are distinct classifications of epilepsy based on the frequency of seizures, which include generalized epilepsy, localized epilepsy, and epilepsy of uncertain origin. Based on the etiology of epilepsy, it is well acknowledged that this condition is characterized by a highly active network that originates from ionic transmission. Brain injury, including traumatic and ischemic injuries, leads to the production of inflammatory chemicals. The excessive production of inflammatory mediators leads to the impairment of the blood-brain barrier (BBB), which induces inflammation in both the central and peripheral regions, leading to epileptic diseases. Over a thousand genes are thought to be involved in developing epilepsy; the most extensively researched genes comprise GABRG2, SCN, CACN, KCN1A, MTHFR, MTTL1, and EFHC1 gene. Various therapeutic approaches have been devised to treat epilepsy, including neurosurgical interventions, antiepileptic medications, anticonvulsant pharmaceuticals, ketogenic dietary regimens, and herbal remedies. This review article provides a thorough analysis of epilepsy, encompassing its categorization, the inflammatory agents accountable for its onset, the genetic factors linked to its progression, and the current therapeutic approaches for this disease.

Keywords: Epilepsy; Gene; Inflammatory mediators; Epileptogenesis; Epileptic seizures; Neurological disorder; Neuroinflammation; Brain.

1. Introduction

Neurological disorders have a consistent influence on individuals of all age groups worldwide. Epilepsy is one of the significant neurological conditions. Various factors, including epilepsy-associated genes, genetic variables, environmental factors such as oxidative stress and depression, and inflammatory molecules, influence epileptic disease (Cárdenas-Rodríguez et al., 2020). Hereditary characteristics are commonly observed within families and account for the bulk of neurological disorders. Certain genetic illnesses are passed down from only one parent, whereas others may have many risk factors (Charzewska et al., 2023). Several neurological diseases are attributed to viral, fungal, and bacterial infections (Wang, 2023). Epilepsy is a neurological illness that results in seizures as a consequence of uncontrolled electrical activity in the brain (Sumadewi, Harkitasari, & Tjandra, 2023). The prevalence of epilepsy is estimated to be 4-10 instances per 1000 individuals, with an annual incidence rate ranging from 50 to 120 cases per 100,000 population (Adamu, Chen, Li, & Xue, 2023). Globally, over 65 million individuals suffer from epilepsy. Most individuals with epilepsy reside in countries with low to intermediate income levels (Billakota, Devinsky, & Kim, 2020). The prevalence of epilepsy in Pakistan is approximately 10 cases per 1000 individuals. The cumulative impact on mental and physical well-being caused by the annual diagnosis of over 100,000 new instances of epilepsy is significant (Billakota et al., 2020).

Various forms of epilepsy are characterized by distinct etiologies. Hyperhomocysteinemia has emerged as a significant causative factor in various neurological illnesses, such as epilepsy and stroke, as well as psychiatric

problems. Between 10% to 40% percent of individuals with epilepsy also exhibit hyperhomocysteinemia (Belcastro et al., 2010). The conversion of homocysteine to methionine is facilitated by folic acid through a series of biochemical reactions, including DNA synthesis, methylation, and methyl group donation. Hyperhomocysteinemia results from reduced folate levels or changes in the enzymes involved in the folate pathway. The presence of autosomal dominant and recessive inheritance patterns in epilepsy exemplifies the intricate nature of the condition, indicating that multiple genes and non-genetic variables play a role in its heritability (Al Mutairi, 2020). Seizures, involuntary movements of the limbs, transient episodes of bewilderment, and various deviations in behavior and emotions characterize epilepsy. The most common manifestation of this illness is epileptic convulsions, which occur due to the interruption of electrical transmission among neurons. Epileptic seizures are clinically evident due to neuronal activity in the brain (Macleod, 2022). Epileptic seizures can be classified as either symptomatic or idiopathic, depending on their cause. Potential causes of symptomatic epilepsy include head trauma, stroke, central nervous system infections (such as brain tumors), and degenerative diseases. On the other hand, idiopathic epilepsy does not have a known cause. Furthermore, the intricate conduct of EP is influenced by the individual's psychological, social, and economic conditions (Anwar et al., 2020).

Studies on epilepsy, conducted on both living species and in laboratory environments, have demonstrated that inflammatory mediators, such as inflammatory chemicals and cells, significantly contribute to the development of epilepsy. The synthesis of High Mobility Group Protein 1, also known as damage-associated molecular pattern and interleukin -1β, can trigger inflammatory responses by stimulated neurons and activated glial cells following pro-convulsive events. Activation of astrocytes and microglia leads to the creation and release of immunological molecules, amplifying subsequent inflammatory cascades (Aronica et al., 2017; Kaur, Patro, Tikoo, & Sandhir, 2015; Webster et al., 2017). Arterioles play a vital role in the blood-brain barrier and thus have a substantial influence on neuroinflammation. Microglial cells, macrophages residing in the brain, serve as an initial line of defense for the central nervous system. An all-encompassing inflammatory illness can promote the development of epilepsy by causing the blood-brain barrier to deteriorate. If there is an increase in the production of these inflammatory mediators, glutamatergic neurons would experience heightened permeability to calcium ions (Ca2+) and display abnormal neuronal hyperexcitability. Astrocyte activation alters energy and glutamate metabolism, resulting in neuronal damage and excessive excitability. The majority of these inflammatory responses result in the recurrence of seizures at a later time (Thurgur & Pinteaux, 2019).

Brain traumas have recently been linked to symptomatic epilepsy, with inflammation playing a crucial part in the development of this condition. Neuroinflammation, whether it is in its acute or chronic form, together with gliosis and microgliosis, as well as latent neuronal abnormalities, collectively contribute to the development of epilepsy (Mukherjee et al., 2020). Repeated seizures are facilitated by the cytokine tumor necrosis factor (TNF), which is involved in the brain's innate and swift neuro-inflammatory reaction to brain damage. The development of epilepsy can be attributed to an elevation in levels of inflammatory mediators, which many neurological disorders can initiate (Soltani Khaboushan, Yazdanpanah, & Rezaei, 2022). Inflammation could occur through the central nervous system (CNS) or a compromised blood-brain barrier (BBB). Neuroinflammation, neuronal loss, and gliosis have been associated with brain regions other than the hippocampus (Cervellati, Trentini, Pecorelli, & Valacchi,

2020). The acute phase of neuroinflammation is linked to a higher likelihood of developing chronic neuroinflammation syndrome. During the acute phase, various events occur, including modifications to receptor modulation, ion channel kinetics, functional protein alterations, and activation of immediate genes (Zhao et al., 2020). Voltage and ligand-gated ion channel dysfunction, particularly in uncommon genetic variants, are significant factors contributing to epilepsy (Süt & Soytürk, 2021).

More than a thousand genes are believed to play a role in the development of epilepsy, and these genes are responsible for encoding ion channel proteins (Oyrer et al., 2018). Pore-forming proteins located in the membrane have the fundamental function of regulating the movement of ions. Examining the genetic factors of different ion channels uncovers a crucial cause-and-effect route that links mutations associated with epilepsy to the occurrence of seizures (Stödberg, 2022). Juvenile myoclonic epilepsy is one of commonly occurring epileptic syndromes that have been associated with alterations in ion channel function (Alehabib et al., 2022). This review article presents a comprehensive examination of epilepsy, including its classification, the inflammatory mediators responsible for its occurrence, the genes associated with epilepsy, and the existing treatments for this condition. In this review paper, the diagrammatic illustrations, including figures 1, 2 and 3, were generated in Adobe Photoshop 2022 with the shape, pen, text, and color fill tools.

1.1. Study Objectives

→ To educate the readers about epilepsy.

→ To elaborate the role of genetics in epileptic disorders.

→ To discuss different types of epilepsy.

→ To discuss metabolic foundations of epilepsy.

→ To educate the readers about available treatments of epilepsy.

2. Types of Epilepsy

There are certain types of epilepsy depending upon seizure occurrence, including generalized epilepsy, focal epilepsy, and unknown epilepsy, discussed below. Figure 1 indicates the flowchart illustration of classification of Epilepsy.

2.1. Generalized Epilepsy

In generalized Epilepsy, people have generalized seizures. Generalized seizures include absence seizure, myoclonic seizure and atonic seizure. Both sides of the brain are affected by these seizures. These seizures are motor or non-motor; motor seizures involve physical movements, and non-motors do not have any movement. Symptoms of motor seizures are myoclonus, twitching, weakness of limbs and low oxygen amount in the brain. Symptoms of non-motor seizures include tiny twitches, frequent eye twitching and stop movements. Mendelian epilepsy syndrome is an example of generalized Epilepsy (Gesche, Christensen, Hjalgrim, Rubboli, & Beier, 2020).

2.2. Focal Epilepsy

In focal epilepsy, people have focal seizures, which can affect only one side of the brain. These seizures begin in one area and move toward other areas. Focal seizures involve both motor and non-motor seizures. Symptoms of
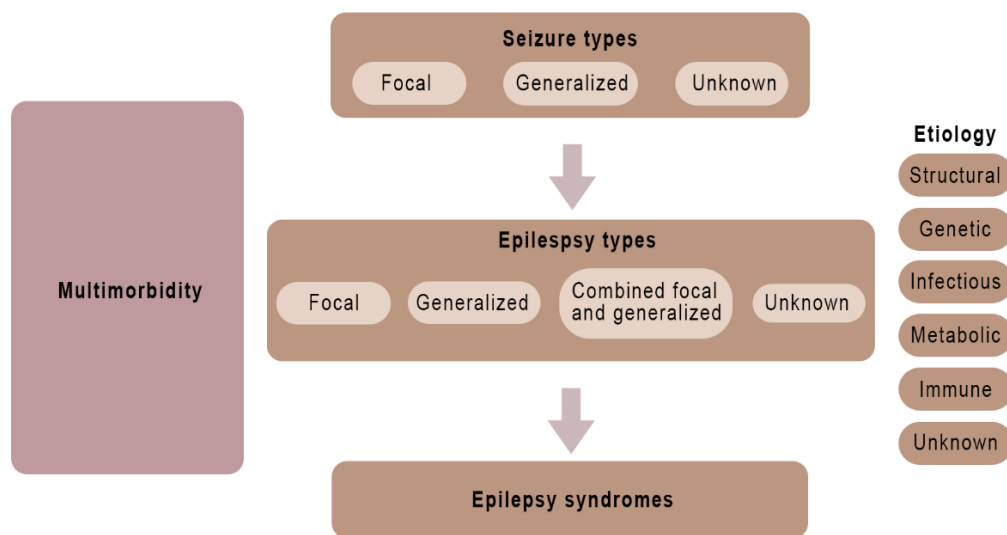
these seizures start with an aura in which someone can feel uneasy in the stomach as well as in riding (Chowdhury, Silva, Whatley, & Walker, 2021). Autosomal dominant nocturnal frontal lobe epilepsy is an example of focal epilepsy (Kurahashi & Hirose, 2018).

2.3. Combined Generalized and Focal Epilepsy

In this type of epilepsy, patients have both generalized and focal seizures. Many reasons become the core cause of combined epilepsy, such as generalized tonic-clonic seizures, myoclonic seizures, absence seizures, tonic seizures, and atonic seizures (Ellis, Ottman, Epstein, Berkovic, & Consortium, 2020).

2.4. Unknown Epilepsy

Sometimes, it is difficult to determine the seizures. In this condition, it is not possible to know which patients have which types of seizures, whether they have focal or generalized seizures (Bai, Zeng, Jia, & Xiao, 2022).
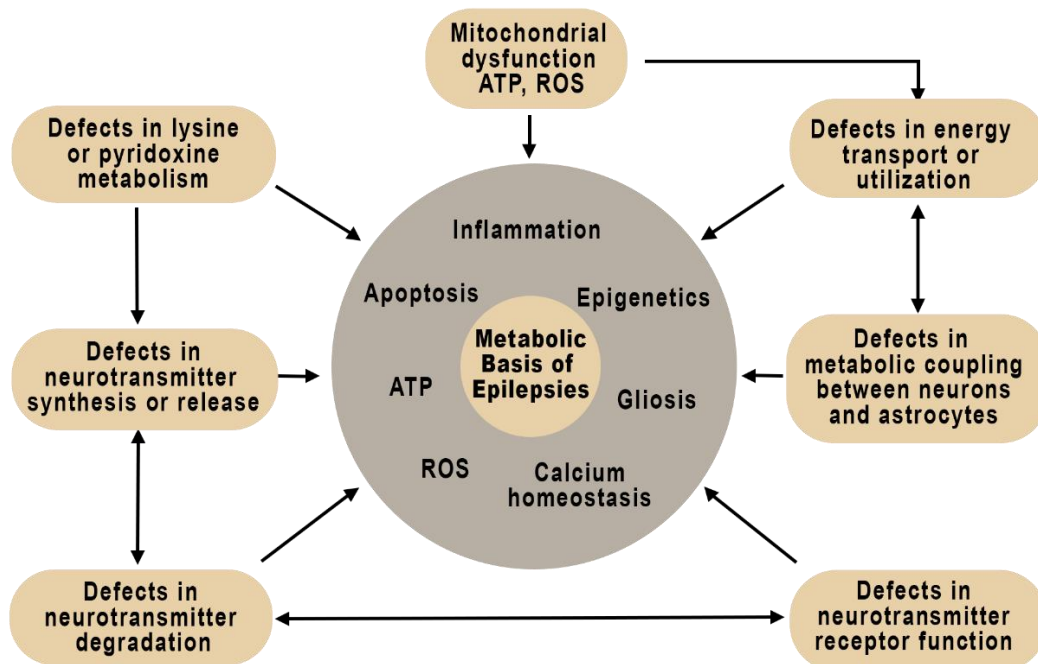

Figure 1. Diagrammatic illustration of classification of Epilepsy

3. Metabolic Basis of Epilepsy

According to the etiology of epilepsy, it has been accepted that this disease has a strong excitability network originating from ionic transmission. Metabolic and bioenergetics changes have been shown in different epilepsy disorders. Their roles remained secondary rather than central (Kovac et al., 2017). Metabolic deregulations are essential in developing brain disorders; for example, the primary characterization of seizures develops epilepsies, which cause an increased periodic energy demand followed by metabolic alterations. As a means to explain the function of metabolism in any state, it is necessary to clarify the exact definition of these mechanisms, which are changed in tissues affected by conditions. Two major metabolic pathways are involved in the metabolic alteration of epilepsies. One is a producing pathway, such as tricarboxylic acid (TCA) cycle oxidative phosphorylation and glycolysis, and the second is redox balance, including nicotinamide adenine dinucleotide phosphate (NAD) (Patel, 2018).

Several known metabolic distresses are enough to start acquired and different genetic epilepsies. Recent research has shown that epileptic seizures and the metabolism of the brain have a complex relation, producing a series of

compounds leading to epilepsy. In addition, metabolism and bioenergetics changes are re-percussion of epilepsy initiated at the synaptic stage. It has been demonstrated that mitochondrial dysfunction causes defects in energy utilization and transport, resulting in metabolic epilepsy (Pearl, Tokatly Latzer, Lee, & Rotenberg, 2023). Lysine and pyridoxine metabolism deficiency limit neurotransmitter synthesis, leading to apoptosis. After the degradation of neurotransmitters occurs, it decreases the function of neurotransmitter receptors, causing calcium homeostasis. Hence, it has been clear that epigenetics, gliosis, inflammation, ROS, and ATP are key components in developing metabolic basis epilepsies (Rho & Boison, 2022). Figure 2 represents a diagrammatic illustration of pathways of the basis of metabolic epilepsy.
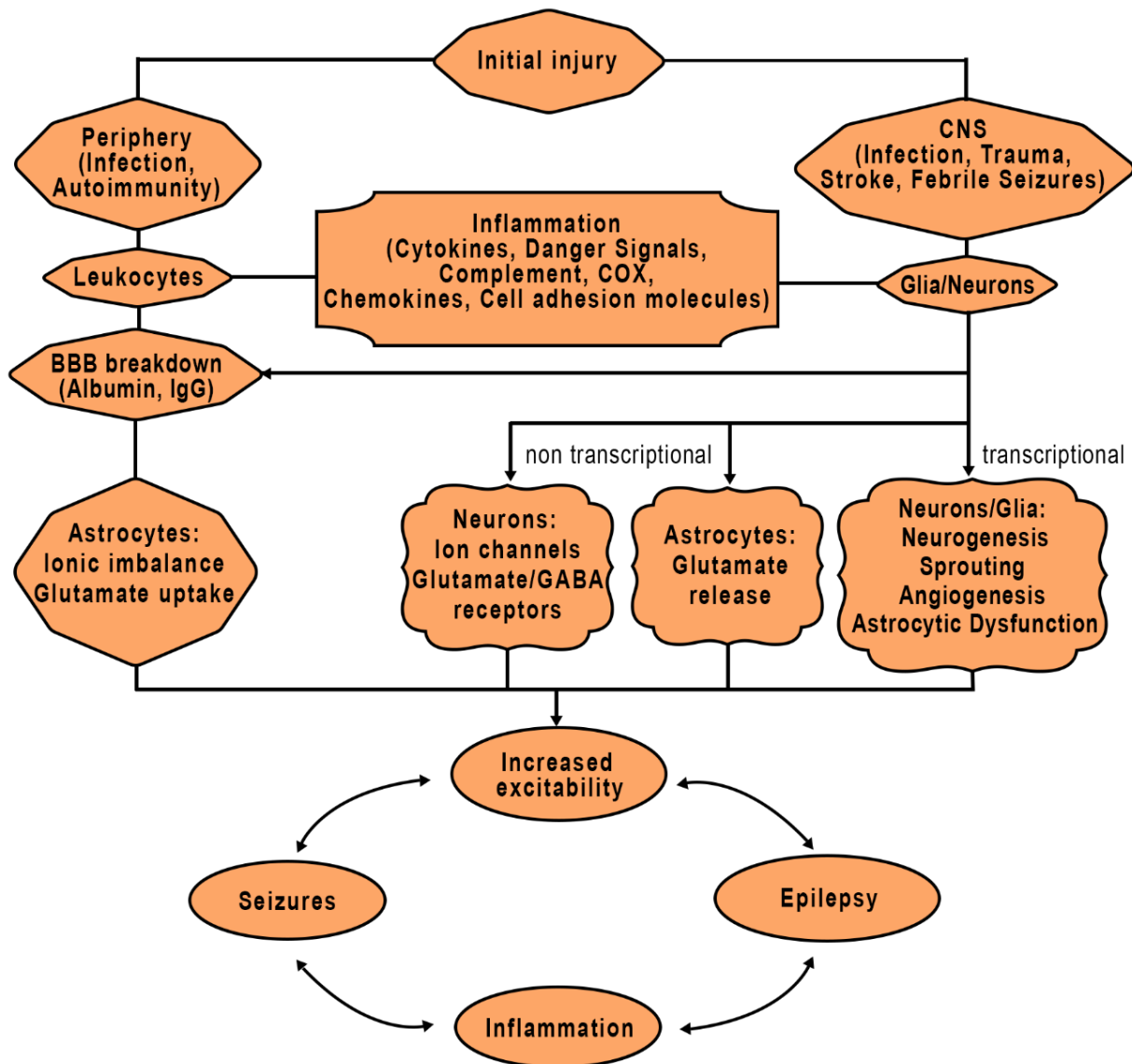

Figure 2. Diagrammatic presentation of pathways of metabolic basis of epilepsies

4. Inflammatory Mediators Causing Epilepsy

An inflammatory mediator is a messenger that initiates an inflammatory action by acting on a cell or blood vessels. Inflammatory molecules are produced due to brain injury, such as traumatic and ischemic injuries. Overexpression of inflammatory mediators causes damage to the blood-brain barrier (BBB), resulting in central and peripheral inflammation (Cash & Theus, 2020). Different inflammatory molecules and their pathways are involved in the development of epilepsy discussed below.

4.1. Mechanism of Inflammatory Mediators

Inflammatory molecules are key components in causing inflammation related to epilepsy. However, the exact pathway of epilepsy is not identified, but blood-brain barrier injuries and inflammation are major factors in epileptic disorders. Inflammation in the brain is induced by specific brain problems, including stroke, seizures, and infection, and these factors are considered significant risk elements for developing epilepsy in humans (Löscher & Friedman, 2020). Figure 3 shows the entire process of inflammatory mediators to cause epilepsy and Table 1 shows different inflammatory mediators involved in neurological and non-neurological diseases.

Figure 3. Diagrammatic presentation of mechanism of inflammatory mediators leading epilepsy

4.1.1. Cytokines

Cytokines are signaling proteins produced by several peripheral immune cells and central nervous system cells, such as interferons, TNF, TGF, chemokines, IL and lymphokines. Under normal conditions, cytokine concentration in the brain is relatively low. However, its amount can be increased when epileptic events occur, like infection, inflammation, stroke, tachypnea, tissue injury, and seizures (Oppenheim, 2020). When the first epileptic seizure occurs, 16 cytokine amount and its associated receptors level are up. The production of the first cytokine signal might initiate and encourage the secondary wave of inflammatory molecules released by neuronal and glial cells and intensify the inflammatory downstream pathways, leading to over-excitation of neurons (Kamali et al., 2021).

4.1.2. Chemokines

Chemokines are the most crucial type of cytokines, which have four further subclasses depending upon their motif structure, known as CX3C, CC, CXC and c. chemokines are associated with G protein-coupled receptors and their expression is influenced by immune cells, including glial cells, endothelial cells and monocytes (Groblewska,

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Litman-Zawadzka, & Mroczko, 2020). Chemokines act as a neuromodulator in the development of different neurological disorders such as Alzheimer's disease, stroke, epilepsy, brain trauma and multiple sclerosis (Kamali et al., 2021).

4.1.3. Interleukin-6

Interleukin-6 is an important pro-inflammatory molecule of the immune system and plays different key roles in the central nervous system (CNS). Expressions of IL-6 and its associated receptor (IL-6R) are initiated by endothelial cells, microglial cells, neuronal cells and astrocytes (Kummer, Zeidler, Kalpachidou, & Kress, 2021). When microglia and astrocytes are activated, IL-6 can be increased. Furthermore, its concentration is also increased with the enhanced production of other cytokines like IL-1B and TNF-α (6). IL-6 is involved in generating epileptogenesis as it has neuroprotective properties. IL-6 has both anti-convulsive and pro-convulsive activities according to its concentration, time period and the effect of other inflammatory mediators (Hayatdavoudi, Hosseini, Hajali, Hosseini, & Rajabian, 2022).

4.1.4. Tumor Necrosis Factor

TNF is an essential protein produced by leukocyte cells, primarily expressed by the blood-brain barrier and glial cells. Expression of TNF- α is possibly induced by 17 activated P2X7Rs and interferon-γ (IFN-γ). Under different conditions of the brain, such as ischemia trauma, neuron lysis, and infection, TNF- α affects cell viability and stimulates fast-changing neuronal excitation. TNF-α function is regulated by its own receptors and different targets immune cells (Souza et al., 2017). There are two types of TNF-α receptors: receptor R1 (TNFR1, p55TNFR), and receptor R2 (TNFR2, p75TNFR); both perform different functions and also plays role in epileptogenesis (Meng & Yao, 2020). P55 receptors of TNF conciliate neuronal loss and nerve cell damage through T cell penetration and microglial activation. P75 receptors activate on blood-brain barrier endothelial cells, enhancing the BBB permeability (McKee & Lukens, 2016).

4.1.5. Tumor growth factor-β

Tumor growth factor- β belongs to the family of tumor necrosis factors. It performs different cell physiological processes such as inflammation, necrosis, cell death, cell migration and expression of extracellular matrix. Different cell factors like proteases and reactive oxygen species (ROS) control the active release of TGF- β, which is also produced by several immune cells. These factors also involved in epilepsy (Cruceriu, Baldasici, Balacescu, & Berindan-Neagoe, 2020).
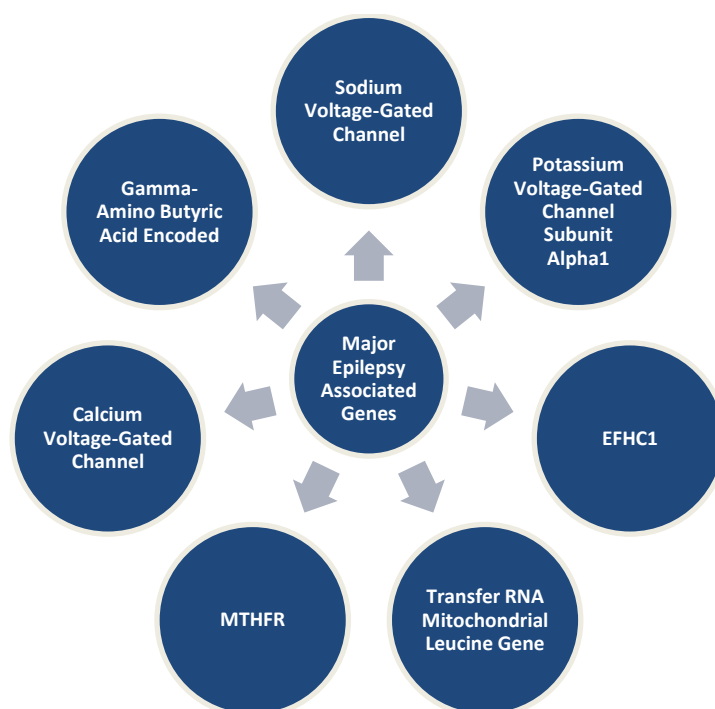
Table 1. Different inflammatory mediators involved in neurological and non-neurological diseases

Type of Disease	Disorder	Inflammatory Mediators
Neurological Diseases	Brain Trauma	HMGB1, IL-1β, IL-6
	Strokes	VCAM, CX3CL1
	Brain Tumors	TLRs, COX, PGs
	Alzheimer's Disease	TNF-α, CXCL8, CCL5

Non-Neurological Diseases	Multiple Sclerosis	T cells, B cells, and macrophages
	Rheumatoid arthritis	TNF-α, IL-1, IL-6
	Type I diabetes	T cells
	Celiac diseases	Interleukin-1β, interferon-γ
	Ulcerative Colitis	Interleukin-5, 13,15
	Hashimoto's thyroiditis	Anti-thyroid antibodies

5. Epilepsy Associated Genes

There are many genes involved in causing different types of epilepsy. Some of the gene candidates involved in causing epilepsy are discussed Below. Figure 4 shows the basic genes involved in causing epilepsy.

Figure 4. Diagrammatic illustration of basic genes involved in causing epilepsy

5.1. GABRG2 Gene

GABA is the primary inhibitory neurotransmitter, also known as gamma-aminobutyric acid, encoded by the GABRG2 gene, mainly found in the mammalian brain and serves as a GABA receptor. GABAA receptors are considered ligand-gated chloride channels, and binding this receptor to its ligand causes chloride ion influx through the ion channel. Dysfunction in GABA receptors causes epilepsy. Increased activation of GABAergic neurotransmission decreases the pacemaking potentials of cells, which limits the ability to produce absence seizures. Febrile seizures (FS) and generalized epilepsy have occurred due to mutations in this gene (Kim, Suh, & Kim, 2021).

5.2. Sodium Voltage Gated Channel (SCN) Gene

Mutations in voltage-gated sodium channels cause myoclonic epilepsy, also known as Dravet syndrome. SCN1A gene variant is associated with this type of epilepsy. These genes are found in different body parts, mainly the central nervous system, Peripheral nervous system, and cardiac and skeletal muscles. Different subunits of sodium voltage-gated channel genes have been expressed in different body regions and cause damage in channels and tissue injury, leading to epilepsy. SCN1A genes are mainly expressed in the central nervous system and maintain neuron excitation by inhibiting the effect of GABA neurons.

Abnormalities in these genes reduce the channel's activity due to inhibition and excitation imbalance (de Lange et al., 2020). SCN2A genes are highly expressed in GABA interneurons and cause migrating focal seizures (Ademuwagun, Rotimi, Syrbe, Ajamma, & Adebiyi, 2021). The SCN3A gene is mainly found in higher concentrations in damaged tissues and is related to sensory neurons that cause pain (Ye et al., 2020).

5.3. Calcium Voltage Gated Channel (CACN) Gene

Calcium channel genes exist in most excited body regions, such as neurons, endocrine, and muscle cells. These genes provide instructions to cells for making calcium channels. They give a proper voltage environment to produce Na, K, and Na-Ca currents in the excitable membranes. However, calcium plays a vital role in regulating different processes, such as cell migration, proliferation, and phagocytosis.

Calcium channel genes are also necessary for neuron excitation, and they regulate shape and time of action potentials. Mutations in these genes area associated with epilepsy (Mayo et al., 2023).

5.4. Potassium Voltage-Gated Channel Subunit Alpha1 A (KCN1A) gene

The potassium channel family is most important among all other channel genes responsible for causing epilepsy. Almost 12 genes of potassium voltage are strongly related to epilepsy (Gao, Lin, Wen, & Jiang, 2022). KCN1A tends to cause changes in membrane potential and is also responsible for developing a neuronal channelopathy known as episodic ataxia type 1 (EA1).

These potassium voltage-related genes are mostly expressed in the brain's hippocampus region. Mutations in these genes are considered to cause benign familial neonatal seizures (BFNS) (Amadori et al., 2022).

5.5. MTHFR Gene

The gene MTHFR may be found on chromosome 1p. Various variations have been identified in the MTHFR gene. The MTHFR mutant homozygous (VV) enzyme contains almost 70% less enzyme production than the standard MTHFR enzyme. The MTHFR C677T polymorphism has been associated with a variety of diseases, including ischemic vascular disease, mental and neurological impairments, including Parkinson's and Alzheimer's disease, and insomnia. The prevalence of the T allele varies widely around the globe (Moll & Varga, 2015).

The relevance of the MTHFR C677T polymorphism in epilepsy susceptibility has shown inconsistent results. There is a relationship between the C677T and the A1298C polymorphism of the gene of MTHFR and epilepsy genetic risk in association with this gene (Rai & Kumar, 2018).

5.6. Transfer RNA Mitochondrial Leucine Gene (MTTL1)

Mutation in transfer RNA mitochondrial leucine gene (MTTL1) and transfer RNA mitochondrial lysine gene (MTTK) are also known to cause epilepsy. Abnormalities in these genes also affect mitochondrial function, resulting in mitochondrial encephalomyopathy. Stroke-like episodes and myoclonic epilepsy are some important types of epilepsy that have occurred due to mutation in MTTL1 and MTTK genes. MTTL1 gives injection for producing a unique type of tRNA designated tRNA LEU, which binds amino acids with proteins to form an assembly. After that, this molecule joins with leucine and is placed in a proper position for growing protein (Sun, Lu, Li, & Wang, 2021).

5.7. EF-Hand Motif-Containing Protein Gene (EFHC1)

Dysfunction in EFHC1 results in neuronal apoptosis associated with juvenile myoclonic epilepsy. This protein is crucial for the regulation of TRPM2 protein. TRPM2 and EFHC1 proteins are simultaneously expressed in the ependymal cells and hippocampus part of the brain. EFHC1 expression is important for the induction of cationic currents and calcium responses through TRPM2 protein in HEK293 cells. Furthermore, TRPM2 susceptibility is increased by EFHC1 protein, resulting in cell death (Suzuki, Inoue, & Yamakawa, 2020).

6. Treatments of Epilepsy

Epilepsy is an incurable disorder because the exact mechanism behind epilepsy causes is still unknown, which makes it complicated to treat epilepsy patients. However, different strategies have been developed to cure epilepsy, like brain surgeries, antileptic drugs, anti-seizure medication, ketogenic diets, and herbal medicines.

6.1. Anti-Epileptic Drugs

Anti-epileptic drugs (AEDs) have been developed to treat epilepsy. These drugs help control 70% of seizures. AEDs mainly regulate the amount of chemicals in the brain that cause seizures. Mostly, these drugs are not effective for epilepsy treatment, but they can stop seizures. There are many AEDs used in daily routine, including:

[1] Topiramate

[2] Lamotrigine

[3] Levetiracetam

[4] Sodium valproate

[5] Carbamazepine

There are some side effects of taking these AEDs regularly, which may appear immediately with AEDs usage or appear after some time, including drowsiness, headache, agitation, lack of energy, and hair loss (Rana, Suman, Veleri, & Punnakkal, 2023).

6.2. Brain Surgery

When AEDs are not working properly, then surgery is the option to remove the infected part of the brain. It is the most complicated procedure, taking several weeks or months to recover. However, there is a risk of memory loss or

other vision problems. These problems may recover with the passage of time or remain permanent (Salem, Chetty, & Chetty, 2023).

6.3. Ketogenic Diet

The ketogenic diet consists of a higher amount of fat and less amount of carbohydrates and protein. This is the most suggested treatment for both adults and children. The ketogenic diet is an essential energy source provided to cells based on low carbohydrates. It is an important antileptic mechanism that increases the production of ATPs to prevent abnormal mitochondrial formation and stimulate mitochondrial biogenesis (El-Rashidy, Nassar, Shokair, & El Gendy, 2023).

6.4. Herbal Therapy

Herbal remedies have been proven to be a more practical approach to cure epilepsy. Most plants contain functional anti-epileptic and anti-convulsant properties, which are beneficial in epilepsy treatment without creating any side effects in the body. Natural chemical compounds improve seizures by regulating the ion channels, maintaining the concentrations of ions in the body, improving the immune system, regulating the dysfunction of mitochondria, and correcting oxidative stress (Zhu et al., 2023). A list of some bioactive compounds is presented in Table 2 based on natural drugs derived from different plant species to treat epilepsy.

Table 2. Natural compounds derived from different plant species to treat epilepsy

Plants/Herbals	Natural Compounds	Mechanism of Action
Camellia sinensis	EGCG	Increase impression of GABA
Cotinus coggygria	Fisetin	Increase GABA level in Brain
Thymus Vulgaris	Terpinene -4-ol	Regulating, GABAergic neurotransmission
Piper nigrum	Piperine	Inhibit TRPV1 receptor
Crocus stivus	Crocin	Suppressing formation of advanced glycation products in brain
Fragrant camphor tea	Borneol	Anti-inflammatory and anti-bacterial activities
Curcuma longa	Curcumin	Anti-inflammatory and neuroprotective activities

7. Challenges

• **Genetic Complexity:** Genetic complexity is one of the main problems in epilepsy research and treatment. The complexity of epilepsy, as it involves several genes, each having varying participation in the condition, makes understanding its exact genetic mechanisms significant. This further complicates its prediction and management, as autosomal dominant and recessive inheritance patterns are unpredictable.

• **Environmental and Metabolic Factors:** Epilepsy is not only a genetic disease; environmental factors such as oxidative stress, infections, and traumatic brain injuries also play an essential role. Also, metabolic disorders,

including hyperhomocysteinemia, promote its development. These factors are variable, and their interplay establishes a multifactorial environment that hinders diagnosis and treatment strategies.

- **Inflammatory Responses:** Another layer of complexity is introduced by the participation of inflammatory mediators in epilepsy. Studying how mediators contribute to the development and recurrence of seizures is a relatively new research field. The problem lies in discovering the particular functions of different inflammatory cytokines and cells and their effect on brain plasticity.

- **Variability in Seizure Types and Symptoms:** Epilepsy can be described in terms of a series of seizure types that have varying manifestations and mechanisms. This variation also poses a challenge in designing the same treatment for all individuals. Personalized medicine has become indispensable but is very difficult to implement and requires in-depth knowledge and the classification for type.

- **Treatment Challenges:** Even though there have been significant improvements in AEDs and surgery, effective treatment of epilepsy somehow continues to pose a challenge. AEDs are not always fully effective and can have severe side effects. Although beneficial to some, surgical interventions are burdened with risks and not suitable for every patient. Besides, new interventions such as ketogenic diets and herbal therapies require further studies to determine their effectiveness and safety.

- **Global Health Disparities:** Epilepsy prevalence, being the highest in low- to middle-income countries, increases difficulties faced by healthcare accessibility and affordability. Resources are limited in these areas, only worsening diagnosis, treatment, and ongoing management of epilepsy, reducing optimal health results.

- **Research Gaps:** Although much progress has been made in epilepsy research, official gaps still exist, especially concerning precise mechanisms operating within the brain during seizure activity. There is a need for further studies that will develop more accurate detection tools, enhance and lessen invasive treatments, and discover the cure.

8. Conclusion

Epilepsy is a prominent neurological disorder caused by a range of factors, including epilepsy-associated genes, hereditary variables, environmental factors such as oxidative stress and depression, and inflammatory molecules that influence it. Several therapeutic methods have been devised to treat epilepsy, including neurosurgical interventions, antiepileptic medications, anticonvulsant pharmaceuticals, ketogenic dietary regimens, and herbal remedies. With a deeper understanding of the genetic, metabolic, and inflammatory pathways, better treatments for epilepsy can be discovered. Adopting innovations such as next-generation sequencing, CRISPR, and enhanced brain imaging with AI could change how we handle epilepsy. The focus on targeted medicine, which is individualized for specific genetic profiles and types of epilepsy, needs to be emphasized. This involves the creation of better anti-epileptic medicines with fewer side effects, as well as perfecting nonpharmacological interventions such as ketogenic diets and neurostimulation therapies. Furthermore, recognizing and addressing the psychosocial effects of epilepsy is essential for obtaining comprehensive care. Epilepsy research should not only focus on biological mechanisms but also strive to improve the lives of the affected. Comprehensively, merging these multiple approaches into one solution for epilepsy patients seems to achieve effective care.

9. Future Directions

The development of understanding and treatment of epilepsy is crucial in a multidisciplinary approach exploring the role of genetic determinants, metabolites acting as mediators, and inflammatory components, along with innovative avenues for therapy. Further researches need to intensify the study of genetic factors leading to epilepsy. These include discovering new genes associated with epilepsy and providing insight into the intricate relationship between these genes and environmental factors. Emerging genetics technologies such as NGS and CRISPR could have significant roles in discovering these genetic secrets and developing precision therapies.

In addition, there is a thorough analysis of epilepsy regarding metabolic aspects. While we comprehend some features of how metabolic modifications contribute to the appearance of seizures, there is a need for additional knowledge in this field. Studies should be done on the mechanism of metabolic deregulations, especially concerning energy use and neurotransmitter generation in seizure formation and propagation. An important aspect will be the role and connection of mitochondrial dysfunction to metabolic epilepsy.

Another possible topic for research is the role of inflammatory mediators in epilepsy. The detailed pathways via which these mediators contribute to the generation and sustenance of seizures should be further investigated in future studies. This includes exposing BBB integrity and operations performed by astrocytes and microglial cells, among other cytokines and chemokines. In addition, the discovery of new anti-inflammatory drugs that could target these pathways with no significant side effects may transform epilepsy treatment.

From the point of view of treatment, a new approach should be made to more personalized medicine. This would entail personalized therapies based on genetic makeup, seizure type, and responses to already-used treatments. It is necessary to research new AEDs that have reduced side effects and high efficacy, especially for drug-resistant epilepsy. Also, other non-pharmacological therapies, such as ketogenic diets and neurostimulation treatments, need more studies to be conducted on them.

The advances in brain imaging and monitoring can allow us to see what happens inside the human brain during a seizure. Artificial Intelligence could be used in developing early seizure prediction systems and responsive neurostimulation devices. Thirdly, it is essential to understand the psychosocial dimensions of epilepsy. Studies should improve the understanding of epilepsy's mental health, quality of life, and socioeconomic effects. However, creating an all-encompassing treatment system that incorporates psychological and social intervention along with medical care will be a priority in providing quality care to people living with epilepsy.

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